DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

93172

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

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CBER - 02 - 010

Warning Letter

MAR 26 2002

Suyu Shu, Ph.D.
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

Dear Dr. Shu:

During an inspection that was conducted between November 5 and November 13, 2001, Ms. Karen M. Kondas and Mr. Steven J. Kilker, investigators with the Food and Drug Administration (FDA), reviewed your conduct of the clinical study entitled ——— This inspection was conducted under the FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

The deficiencies noted during the inspection are listed on the Form FDA 483 that was issued to and discussed with you at the conclusion of the inspection.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to fulfill the general responsibilities of investigators. [21 CFR § 312.60 and Part 50].**

   An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. Our

investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of investigational new drugs in that you failed to follow the investigational plan and to adequately protect the rights, safety, and welfare of subjects as described below.

2. **You failed to conduct an investigation according to the signed investigational plan (protocol). [21 CFR § 312.60].**

A. You did not perform the protocol-required tests for endotoxin and mycoplasma prior to the infusion of the investigational ——— for all study subjects. Failure to perform the quality control tests places subjects at increased risk.

B. The protocol does not allow the addition of antibiotic ——— . to the culture medium used to prepare the final dose of the investigational activated ——— During the inspection, you acknowledged the addition of ——— to the culture medium. Furthermore, none of the enrolled subjects were screened for a history of possible allergic reactions to ——— or related antibiotics.

C. The protocol and the amendments require the ——— , to be ——— ——— . before subsequent infusion to the subjects. For all the subjects who were administered the ——— . vaccines, the dose of ——— administered to the ——— could not be determined for each initial and booster injections of ———

D. Your laboratory's written study procedures were changed so that ——— ——— were to be exposed to ——— . During the inspection you explained that the dosage of ——— is for booster vaccinations ———
This revision in protocol was neither submitted to the Institutional Review Board nor approved by the sponsor.

E. There is no record that you validated the irradiator to verify accuracy of the radiation dose administered to the ——— In addition, it is not possible to verify that the ——— were exposed to sufficient radiation to render them incapable of further proliferation.

F. You failed to follow the protocol amendments dated 1/26/99 and 9/8/99 that require the booster vaccinations with autologous irradiated ——— ——— to be administered with ——— Subjects ——— received multiple booster vaccinations without the co-administration of ———

G. The protocol requires the preparation of the [redacted] vaccine and [redacted] to be performed under sterile conditions. You cannot confirm that aseptic procedures were used in the study as you failed to validate the equipment, [redacted] where the investigational product was processed.

H. You enrolled subject [redacted] who did not meet the study inclusion criteria. The protocol requires previous radiation therapy to be completed at least 28 days prior to the vaccination with autologous [redacted]. Subject [redacted] received photon beam radiation from 8/31/99 to 9/16/99 and was administered the autologous [redacted] vaccine on 10/4/99, 18 days later.

3. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].**

A. You failed to obtain the informed consent for four subjects before conducting the study related tests. You performed the protocol-required anergy tests for subjects [redacted], and the test for Human Immunodeficiency Virus for subject [redacted], without a signed informed consent from the subjects.

B. The consent form approved on 2/19/99 by the Cleveland Clinic Foundation IRB was revised to include a description of the booster vaccinations. Subject [redacted], signed an earlier version of the consent form that did not describe the booster vaccinations. Subject [redacted] received three booster vaccinations on 5/18/99, 6/26/99, and 8/24/99 before signing the current version of the consent form on 10/7/99.

4. **You failed to prepare and maintain adequate and accurate case histories. [21 CFR § 312.62 (b)].**

A. You failed to record all data pertinent to the investigation, for example, the radiation dose administered to the [redacted] in the case histories for all study subjects. We note that three days before the start of the inspection, you prepared retrospective summaries of manufacturing steps for each subject, including a radiation dose of [redacted] for the initial and booster [redacted] vaccine. This radiation dose record cannot be verified by source documents.

B. There are deficiencies in your record-keeping practices. All records for the manufacture of the investigational [redacted] vaccine and [redacted] were written in pencil, and many entries are illegible. Furthermore, there is no documentation of the name or initials of the person making entry in the manufacturing records.

5. **You failed to report all unanticipated problems involving risks to human subjects to the Institutional Review Board (IRB). [21 CFR § 312.66].**

   A. Subject — was administered the booster vaccination on 5/18/99 and developed a grade 3 sepsis. You did not report this serious adverse experience (SAE) to the IRB.

   B. Subject — received the investigational product on 9/10/99 and developed a grade 3 fever and a significant elevation in systolic blood pressure subsequent to the — infusion that required hospitalization. Both SAEs were unanticipated according to the protocol and the consent form. You did not report both SAEs to the IRB. Dr. Cohen, a co-investigator for the study, acknowledged the violation during the discussion with the FDA investigators.

6. **You failed to ensure that all changes in research activity are approved by the IRB. [21 CFR § 312.66].**

   As stated in item 2F above, you administered the booster vaccinations to three subjects without —— For the booster vaccinations, the approved protocol amendments dated 1/26/99 and 9/8/99 require and the consent forms approved by the IRB on 2/19/99, 1/8/00, and 1/8/01 advise that there will be co-administration of ———— to the subjects. You failed to get an approval from the IRB for the revision in protocol regarding administration of booster vaccinations without ————

You are currently involved in at least eight clinical studies. In your response, please explain the changes you have implemented in ongoing studies to assure that they are conducted in compliance with 21 CFR Parts 50 and 312.

This letter is not intended to be an all-inclusive list of deficiencies in your clinical study of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you have taken to correct these violations and to prevent the recurrence of similar violations in future studies. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

Bhanu Kannan (HFM-664)
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA Cincinnati District Office at the address listed below.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

[redacted]